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Brian C. Remy
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Date: December 2, 2004

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Group: 1614

Alexander Mayweg, et al.

Serial No.: 10/743,642

Filed: December 22, 2003

For: **NOVEL CB1 RECEPTOR INVERSE AGONISTS**

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December 2, 2004

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Attached please find the certified copy of the foreign application from which priority is claimed for this case:

Country	Application No.	Filing Date
Europe	03000003.8	January 2, 2003

Respectfully submitted,

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The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

03000003.8

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For the President of the European Patent Office

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Anmeldung Nr:
Application no.: 03000003.8
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Anmelder/Applicant(s)/Demandeur(s):

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SUISSE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Novey pyrrole and imidazole derivatives

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

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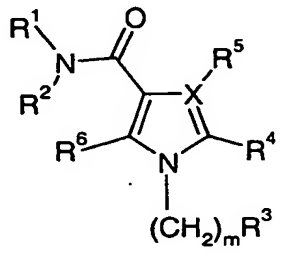
F. Hoffmann-La Roche AG, CH-4070 Basle, Switzerland

Case 21554

Novel Pyrrole and Imidazole Derivatives

The present invention is concerned with novel pyrrole and imidazole derivatives, their manufacture, pharmaceutical compositions containing them and their use as medicaments. The active compounds of the present invention are useful in treating obesity and other disorders.

In particular, the present invention relates to compounds of formula (I):



(I)

wherein

X is C or N ;

R^1 is hydrogen or lower alkyl;

R^2 is lower alkyl or $-(CH_2)_n-R^{2a}$;

R^{2a} is cycloalkyl, optionally mono-, di-, tri- or tetra-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, fluorinated lower alkyl or fluorinated lower alkoxy; a 5- or 6-membered monovalent saturated heterocyclic ring containing one to three heteroatoms independently selected from nitrogen, oxygen and sulfur, said heterocyclic ring being optionally mono-, di- or tri-substituted, independently, by hydroxy, lower

alkyl, lower alkoxy, amino, lower alkylamino, oxo, fluorinated lower alkyl or fluorinated lower alkoxy; a 5- or 6-membered monovalent heteroaromatic ring containing one to four heteroatoms independently selected from nitrogen, oxygen and sulfur, said heteroaromatic ring being optionally mono-, di- or tri-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, halogen, amino, lower alkylamino or cycloalkyl; or phenyl, which may optionally be mono-, di- or tri-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, halogen, lower alkylamino, halogenated lower alkyl, halogenated lower alkoxy or nitro;

R^3 is cycloalkyl, optionally mono-, di-, tri- or tetra-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, fluorinated lower alkyl or fluorinated lower alkoxy; or phenyl, which may optionally be mono-, di- or tri-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, halogen, lower alkylamino, halogenated lower alkyl, halogenated lower alkoxy or nitro;

R^4 is a 5- or 6-membered monovalent heteroaromatic ring containing one to three heteroatoms independently selected from nitrogen, oxygen and sulfur, said heteroaromatic ring being optionally mono-, di- or tri-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, halogen, amino, lower alkylamino; naphthyl, which may optionally be mono-, di- or tri-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, halogen, lower alkylamino, halogenated lower alkyl, halogenated lower alkoxy or nitro; or phenyl which may optionally be mono-, di- or tri-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, halogen, nitro, halogenated lower alkyl, halogenated lower alkoxy, cyano, lower alkylsulfonyl or $-NR^7R^8$; or two adjacent substituents of the said phenyl residue together are $-O-(CH_2)_p-O-$ or $-(CH_2)_2-C(O)NH-$;

R^5 and R^6 are each independently hydrogen, lower alkyl, halogen or fluorinated methyl;

R^7 and R^8 are each independently hydrogen or lower alkyl; or R^7 and R^8 together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated or aromatic heterocyclic ring optionally containing one or two further heteroatoms independently selected from nitrogen, oxygen and sulfur, said saturated or aromatic heterocyclic ring being optionally substituted by hydroxy, lower alkyl, lower alkoxy, halogen, amino or lower alkylamino;

m is 0, 1 or 2;

n is 0 or 1;

p is 1, 2 or 3;

and pharmaceutically acceptable salts thereof.

Two different subtypes of cannabinoid receptors (CB_1 amd CB_2) have been isolated and both belong to G protein coupled receptor superfamily. An alternative spliced form of CB_1, CB_{1A}, has also been described, but it did not exhibit different properties in terms of ligand binding and receptor activation than CB_1 (D.Shire, C. Carrillon, M. Kaghad, B. Calandra, M. Rinaldi-Carmona, G. Le Fur, D. Caput, P. Ferrara, J. Biol. Chem. 270 (8) (1995) 3726-31). The CB_1 receptor is mainly located in the brain, whereas the CB_2 receptor is predominately distributed in the peripherie primarily localized in spleen and cells of the immune system (S. Munro, K.L. Thomas, M. Abu-Shaar, Nature 365 (1993) 61-61). Therefore in order to avoid side effects a CB_1-selective compound is desirable.

Δ^9-tetrahydrocannabinol (Δ^9-THC) is the principal psychoactive compound in the Indian hemp (Y. Gaoni, R. Mechoulam, J. Am. Chem. Soc., 86 (1964) 1646), *canabis savita* (marijuanan), which is used in medicine since ages (R. Mechoulam (Ed.) *in "Cannabinoids as therapeutic Agents"*, 1986, pp. 1-20, CRC Press). Δ^9-THC is a non-selective $CB_1/_2$ receptor agonist and is available in the USA as dronabinol (marinol®) for the alleviation of cancer chemotherapy-induced emesis (CIE) and the reversal of body weight loss experienced by AIDS patients through appetite stimulation. In the UK Nabolinone (LY-109514, Cesamet®), a synthetic analogue of Δ^9-THC, is used for CIE (R. G. Pertwee, Pharmaceut. Sci. 3 (11) (1997) 539-545, E. M. Williamson, F. J. Evans, Drugs 60 (6) (2000) 1303-1314).

Anandamide (arachidonylethanolamide) was identified as the endogenous ligand (agonist) for CB_1 (R.G. Pertwee, Curr. Med. Chem., 6 (8) (1999) 635-664;W.A. Devane, L. Hanus, A. Breuer, R.G. Pertwee, L.A. Stevenson, G. Griffin, D. Gibson, A. Mandelbaum, A. Etinger, R. Mechoulam, Science 258 (1992) 1946-9). Anandamide and 2-arachidonoylglycerol (2-AG) modulate at the presynaptic nerve teminal negatively adenylate cyclase and voltage-sensitive Ca^{2+} channels and activates the inwardly rectifying K^+ channel (V. Di Marzo, D. Melck, T. Bisogno, L. De Petrocellis, Trends in Neuroscience 21 (12) (1998) 521-8), thereby affecting neurotransmitter release and/or action, which decreases the release of neurotransmitter (A. C. Porter, C.C. Felder, Pharmacol. Ther., 90 (1) (2001) 45-60).

Anandamide as Δ^9-THC also increases feeding through CB_1 receptor-mediated mechanism. CB_1 selective antagonists block the increase in feeding associated with administration of anandamide (C.M. Williams, T.C. Kirkham, Psychopharmacology 143 (3) (1999) 315-317; C. C. Felder, E. M. Briley, J. Axelrod, J. T. Simpson, K. Mackie, W. A. Devane, Proc. Natl. Acad. Sci. U. S. A. 90 (16) (1993) 7656-60) and caused appetite suppression and weight loss (G. Colombo, R. Agabio, G. Diaz, C. Lobina, R. Reali, G. L. Gessa, Life Sci. 63 (8) (1998) L113-PL117).

Leptin is the primary signal through which the hypothalamus senses nutritional state and modulates food intake and energy balance. Following temporary food restriction, CB1 receptor knockout mice eat less than their wild-type littermates, and the CB1 antagonist SR141716A reduces food intake in wild-type but not knockout mice. Furthermore, defective leptin signaling is associatedd with elevated hypothalamic, but not cerebellar, levels of endocannabinoids in obese db/db and ob/ob mice and Zucker rats. Acute leptin treatment of normal rats and ob/ob mice reduces anandamide and 2-arachidonoyl glycerol in the hypothalamus. These findings indicate that endocannabinoids in the hypothalamus may tonically activate CB1 receptors to maintain food intake and form part of the neural circuitry regulated by leptin (V. Di Marzo, S. K. Goparaju, L. Wang, J. Liu, S. Bitkai, Z. Jarai, F. Fezza, G. I. Miura, R. D. Palmiter, T. Sugiura, G. Kunos, Nature 410 (6830) 822-825).

SR-141716A, a CB1 selective antagonist / inverse agonist is undergoing currently phase III clinical trials for the treatment of obesity. In a double blind placebo-controlled study, at the doses of 5, 10 and 20 mg daily, SR 141716 significantly reduced body weight when compared to placebo (F. Barth, M. Rinaldi-Carmona, M. Arnone, H. Heshmati, G. Le Fur, *"Cannabinoid antagonists: From research tools to potential new drugs."* Abstracts of Papers, 222nd ACS National Meeting, Chicago, IL, United States, August 26-30, 2001).

Other compounds which have been proposed as CB1 receptor antagonists respectively inverse agonists are aminoalkylindols (AAI; M. Pacheco, S. R. Childers, R. Arnold, F. Casiano, S. J. Ward, J. Pharmacol. Exp. Ther. 257 (1) (1991) 170-183), like 6-bromo- (WIN54661; F. M. Casiano, R. Arnold, D. Haycock, J. Kuster, S. J. Ward, NIDA Res. Monogr. 105 (1991) 295-6) or 6-iodopravadoline (AM630, K. Hosohata, R. M. Quock, R.M; Hosohata, T. H. Burkey, A. Makriyannis, P. Consroe, W. R. Roeske, H. I. Yamamura, Life Sci. 61 (1997) 115 – 118; R. Pertwee, G. Griffin, S. Fernando, X. Li, A. Hill, A. Makriyannis, Life Sci. 56 (23-24) (1995) 1949-55). Arylbenzo[b]thiophene and benzo[b]furan (LY320135, C. C. Felder, K. E. Joyce, E. M. Briley, M. Glass, K. P. Mackie,

K. J. Fahey, G. J. Cullinan, D. C. Hunden, D. W. Johnson, M. O. Chaney, G. A. Koppel, M. Brownstein, J. Pharmacol. Exp. Ther. 284 (1) (1998) 291-7) disclosed in WO9602248, US5596106, 3-alkyl-(5,5-diphenyl)imidazolidinediones (M. Kanyonyo, S. J. Govaerts, E. Hermans, J. H. Poupaert, D. M. Lambert, Bioorg. Med. Chem. Lett. 9 (15) (1999) 2233 – 2236.) as well as 3-alkyl-5-arylimidazolidinediones (F. Ooms, J. Wouters, O. Oscaro. T. Happaerts, G. Bouchard, P.-A. Carrupt, B. Testa, D. M. Lambert, J. Med. Chem. 45 (9) (2002) 1748-1756) are known to antagonize the CB_1 receptor respectively act as an inverse agonist on the hCB_1 receptor. WO0015609 (FR2783246-A1), WO0164634 (FR2805817-A1), WO0228346, WO0164632 (FR2805818-A1), WO0164633 (FR2805810-A1) disclosed substituted 1-bis(aryl)methyl-azetidines derivatives as antagonists of CB_1. In WO0170700 4,5-dihydro-1H-pyrazole derivatives are described as CB_1 antagonists. In several patents bridged and non-bridged1,5-diphenyl-3-pyrazolecarboxamide derivatives are disclosed as CB_1 antagonists/inverse agonists (WO0132663, WO0046209, WO9719063, EP658546, EP656354, US5624941, EP576357, US3940418).

It is an object of this invention to provide selective, directly acting CB1 receptor antagonists respectively inverse agonists. Such antagonists / inverse antagonists are useful in medical therapy, particularly in the treatment and/or prevention of diseases which are associated with the modulation of CB1 receptors.

Unless otherwise indicated, the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

In this specification the term "lower" is used to mean a group consisting of one to eight, preferably of one to four carbon atom(s).

The term "halogen" refers to fluorine, chlorine, bromine and iodine, preferably to chlorine and fluorine.

The term "alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of one to twenty carbon atoms, preferably one to sixteen carbon atoms, more preferably one to ten carbon atoms.

The term "lower alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent alkyl radical of one to eight carbon atoms, preferably one to four carbon atoms. This term is further exemplified by radicals such as methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, isobutyl, t-butyl, n-pentyl, 3-methylbutyl, n-hexyl, 2-ethylbutyl and the like.

The term "alkoxy" refers to the group R'-O-, wherein R' is alkyl. The term "lower alkoxy" refers to the group R'-O-, wherein R' is lower alkyl. Examples of lower alkoxy groups are e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy and hexyloxy, with methoxy being especially preferred.

The term "lower alkylamino" refers to the group R'-NH-, wherein R' is lower alkyl.

The term "lower alkylsulfonyl" refers to the group R'-$S(O)_2$-, wherein R' is lower alkyl.

The term "halogenated lower alkyl" refers to a lower alkyl group wherein at least one of the hydrogens of the lower alkyl group is replaced by a halogen atom, preferably fluoro or chloro. Among the preferred halogenated lower alkyl groups are trifluoromethyl, difluoromethyl, fluoromethyl and chloromethyl, with trifluoromethyl being especially preferred. The term "fluorinated lower alkyl" refers to a lower alkyl group wherein at least one of the hydrogens of the lower alkyl group is replaced by fluoro. Among the preferred fluorinated lower alkyl groups are trifluoromethyl, difluoromethyl and fluoromethyl, with trifluoromethyl being especially preferred.

The term "halogenated lower alkoxy" refers to a lower alkoxy group wherein at least one of the hydrogens of the lower alkoxy group is replaced by halogen, preferably by fluorine or chlorine. Among the preferred halogenated lower alkoxy groups are fluorinated lower alkoxy groups such as trifluoromethoxy, difluoromethoxy and fluoromethoxy, with trifluoromethoxy being especially preferred. The term "fluorinated lower alkoxy" refers to a lower alkoxy group wherein at least one of the hydrogens of the lower alkoxy group is replaced by fluoro. Among the preferred fluorinated lower alkoxy groups are trifluoromethoxy, difluoromethoxy and fluoromethoxy, with trifluoromethoxy being especially preferred.

The term "cycloalkyl" refers to a monovalent carbocyclic radical of three to six, preferably three to five carbon atoms. This term is further exemplified by radicals such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "pharmaceutically acceptable salts" embraces salts of the compounds of formula (I) with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, fumaric acid, succinic acid, tartaric acid, methanesulphonic acid, salicylic acid, p-toluenesulphonic acid and the like, which are non toxic to living organisms. Preferred salts with acids are formates, maleates, citrates, hydrochlorides, hydrobromides and methanesulfonic acid salts, with hydrochlorides being especially preferred.

In one embodiment, the present invention relates to a compound of formula (I) as defined above, wherein R^1 is hydrogen or lower alkyl.

Preferable lower alkyl residues R^1 are methyl and ethyl, with methyl being especially preferred. Most preferably, R^1 is hydrogen.

In another embodiment, the present invention relates to a compound of formula (I) as defined above, wherein R^2 is lower alkyl or $-(CH_2)_n-R^{2a}$.

Preferable lower alkyl residues R^2 are branched or straight chain alkyl residues with one to eight, preferably three to five carbon atoms, such as n-propyl, isopropyl, n-butyl, s-butyl, isobutyl, n-pentyl and 2-ethylhexyl. Most preferred lower alkyl residues R^2 are n-propyl, n-butyl, s-butyl, isobutyl and n-pentyl, with n-butyl being especially preferred. Preferable residues $-(CH_2)_n-R^{2a}$ are those wherein n is 0 and R^{2a} is as defined below.

In one embodiment, R^{2a} is cycloalkyl, optionally mono-, di-, tri- or tetra-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, fluorinated lower alkyl or fluorinated lower alkoxy; a 5- or 6-membered monovalent saturated heterocyclic ring containing one to three heteroatoms independently selected from nitrogen, oxygen and sulfur, said heterocyclic ring being optionally mono-, di- or tri-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, amino, lower alkylamino, oxo, fluorinated lower alkyl or fluorinated lower alkoxy; a 5-or 6-membered monovalent heteroaromatic ring containing one to four heteroatoms independently selected from nitrogen, oxygen and sulfur, said heteroaromatic ring being optionally mono-, di- or tri-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, halogen, amino, lower alkylamino or cycloalkyl; or phenyl, which may optionally be mono-, di- or tri-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, halogen, lower alkylamino, halogenated lower alkyl, halogenated lower alkoxy or nitro.

Preferable cycloalkyl residues R^{2a} are cycloalkyl residues with three to six carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, which may optionally be mono-, di-, tri- or tetra-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, fluorinated lower alkyl or fluorinated lower alkoxy, preferably by lower alkyl, such as methyl, and/or hydroxy. Most preferable cycloalkyl residues R^{2a} are unsubstituted cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, with cyclohexyl being especially preferred. Preferable heterocyclic rings R^{2a} are 5- or 6-memberd, with 5-membered being especially preferred, and contain one to three, preferably one or two, heteroatoms independently selected from nitrogen, oxygen and sulfur, preferably selected form nitrogen and oxygen, said heterocyclic ring being optionally mono-, di- or tri-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, amino, lower alkylamino, oxo, fluorinated lower alkyl or fluorinated lower alkoxy. Examples of heterocyclic rings R^{2a} are tetrahydrofuranyl, piperidinyl and isoxazolyl, optionally substituted as defined above. Preferably, heterocyclic rings R^{2a} are unsubstituted or substituted by lower alkyl, such as methyl, or by oxo. Most preferred heterocyclic rings R^{2a} are tetrahydrofuranyl, 2,2-dimethyl-tetrahydrofuranyl, piperidinyl and isoxazolidinone. Preferable heteroaromatic rings R^{2a} are 5- or 6-membered and contain one to four, preferably one, two or four, heteroatoms independently selected from nitrogen, oxygen and sulfur, said heteroaromatic ring being optionally mono-, di- or tri-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, halogen, amino, lower alkylamino or cycloalkyl. Examples of heteroaromatic rings R^{2a} are thienyl, furyl, tetrazolyl, imidazolyl and pyrazolyl, optionally substituted as defined above. Preferably, heteroaromatic rings R^{2a} are unsubstituted or mono-substituted by lower alkyl, such as methyl, or by cycloalkyl, such as cyclopropyl. Most preferable heteroaromatic rings R^{2a} are thienyl, furyl, 2-methyl-furyl, tetrazolyl, imidazolyl and 3-cyclopropyl-pyrazolyl. Preferable phenyl residues R^{2a} are optionally mono-, di- or tri-substituted, preferably mono- or di-substituted, independently, by lower alkoxy, such as methoxy, halogen, such as chloro, halogenated lower alkyl, such as trifluoromethyl, halogenated lower alkoxy, such as trifluoromethoxy, or nitro. Most preferable phenyl residues R^{2a} are unsubstituted phenyl, 4-trifluoromethyl-phenyl, 4-chloro-phenyl, 3,4-dichloro-phenyl, 3,4-dimethoxy-phenyl, 2-nitro-phenyl and 4-trifluoromethoxy-phenyl.

In another embodiment, the present invention relates to a compound of formula (I) as defined above, wherein R^3 is cycloalkyl, optionally mono-, di-, tri- or tetra-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, fluorinated lower alkyl or fluorinated lower alkoxy; or phenyl, which may optionally be mono-, di- or tri-substituted,

independently, by hydroxy, lower alkyl, lower alkoxy, halogen, lower alkylamino, halogenated lower alkyl, halogenated lower alkoxy or nitro.

Preferable cycloalkyl residues R^3 are cycloalkyl residues with three to six carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, which may optionally be mono-, di-, tri- or tetra-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, fluorinated lower alkyl or fluorinated lower alkoxy, preferably by lower alkyl, such as methyl, and/or hydroxy. Most preferable cycloalkyl residues R^3 are unsubstituted cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, with cyclohexyl being especially preferred. Preferable phenyl residues R^3 are optionally mono-, di- or tri-substituted, preferably mono- or di-substituted, independently, by lower alkoxy, such as methoxy, halogen, such as chloro, halogenated lower alkyl, such as trifluoromethyl, halogenated lower alkoxy, such as trifluoromethoxy, or nitro. Most preferable phenyl residues R^{2a} are unsubstituted phenyl, 4-trifluoromethyl-phenyl, 4-chloro-phenyl, 3,4-dichloro-phenyl, 3,4-dimethoxy-phenyl, 2-nitro-phenyl and 4-trifluoromethoxy-phenyl.

In another embodiment, the present invention relates to a compound of formula (I) as defined above, wherein R^4 is a 5- or 6-membered monovalent heteroaromatic ring containing one to three heteroatoms independently selected from nitrogen, oxygen and sulfur, said heteroaromatic ring being optionally mono-, di- or tri-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, halogen, amino, lower alkylamino; naphthyl, which may optionally be mono-, di- or tri-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, halogen, lower alkylamino, halogenated lower alkyl, halogenated lower alkoxy or nitro; or phenyl which may optionally be mono-, di- or tri-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, halogen, nitro, halogenated lower alkyl, halogenated lower alkoxy, cyano, lower alkylsulfonyl or $-NR^7R^8$; or two adjacent substituents of the said phenyl residue together are $-O-(CH_2)_p-O-$ or $-(CH_2)_2-C(O)NH-$. Preferable heteroaromatic rings R^4 are 5- or 6-membered, preferably 6-membered, and contain one to three, preferably one or two, heteroatoms independently selected from nitrogen, oxygen and sulfur, preferably nitrogen, said heteroaromatic ring being optionally mono-, di- or tri-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, halogen, amino or lower alkylamino. Examples of heteroaromatic rings R^4 are pyridinyl, pyrimidinyl and pyrazinyl, preferably pyridinyl and pyrazinyl, optionally substituted as defined above. Preferably, heteroaromatic rings R^4 are unsubstituted or mono-substituted by lower alkyl, such as methyl and ethyl. Most preferable heteroaromatic rings R^4 are pyridinyl, pyrazinyl, 4-methyl-pyridinyl, 3-methyl-pyrazinyl, 3-ethyl-pyrazinyl and 3,5-dimethyl-pyrazinyl. Preferably, naphthyl residues R^4 are

unsubstituted. Preferable phenyl residues R^4 are optionally mono-, di- or tri-substituted, independently, by hydroxy, lower alkyl, such as methyl and t-butyl, lower alkoxy, such as methoxy, halogen, such as chloro, fluoro and bromo, nitro, halogenated lower alkyl, such as trifluoromethyl, halogenated lower alkoxy, such as di- and trifluoromethoxy, cyano, lower alkylsulfonyl, such as methylsulfonyl, or by $-NR^7R^8$, wherein R^7 and R^8 are as defined below; or two adjacent substituents of the said phenyl residue together are $-O-(CH_2)_p-O-$ or $-(CH_2)_2-C(O)NH-$, and p is 1, 2 or 3, preferably 2 or 3.

Preferable $-NR^7R^8$ substituents of a phenyl residue R^4 are those wherein R^7 and R^8 are each independently hydrogen or lower alkyl, such as methyl and ethyl. Preferably, both R^7 and R^8 are methyl or both R^7 and R^8 are ethyl. Further preferable $-NR^7R^8$ substituents of a phenyl residue R^4 are those wherein R^7 and R^8 together with the nitrogen atom to which they are attached form a 5- or 6-membered, preferably 5-membered, saturated or aromatic, preferably saturated, heterocyclic ring optionally containing one or two, preferably one, further heteroatom(s) independently selected from nitrogen, oxygen and sulfur, preferably selected from nitrogen and oxygen, said saturated or aromatic heterocyclic ring being optionally mono- or di-substituted, preferably mono-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, halogen, amino or lower alkylamino, preferably by lower alkyl, such as methyl. Preferably, the said saturated or aromatic heterocyclic ring formed by R^7 and R^8 together with the nitrogen atom to which they are attached is unsubstituted and does not contain any furter heteroatom. Most preferable saturated or aromatic heterocyclic ring formed by R^7 and R^8 together with the nitrogen atom to which they are attached are pyrrolidinyl, piperidinyl, piperazinyl, 4-methyl-piperazinyl, imidazolyl, and morpholino, with pyrrolidinyl being especially preferred. Preferably, $-NR^7R^8$ substituents of a phenyl residue R^4 are at the para-position. Most preferable phenyl residues R^4 are mono- or di-substituted, independently, by halogen, such as chloro and fluoro, halogenated lower alkyl, such as trifluoromethyl, lower alkoxy, such as methoxy, or mono-substituted at the para-position by a residue $-NR^7R^8$, preferably by pyrrolidinyl.

In another embodiment, the present invention relates to a compound of formula (I) as defined above, wherein R^5 and R^6 are each independently hydrogen, lower alkyl, halogen or fluorinated methyl.

Preferable lower alkyl residues R^5 and R^6 are methyl and ethyl, with methyl being especially preferred. Preferable halogen residues R^5 and R^6 are fluoro and chloro, with chloro being especially preferred. Preferable residue R^5 is lower alkyl, such as methyl. Preferable residues R^6 are hydrogen and lower alkyl, such as methyl.

In one embodiment of the present invention X is C. In another embodiment of the present invention X is N.

Preferably, m is 0 or 1, more preferably m is 1.

Preferably, n is 0 or 1, more preferably n is 0.

Preferably, p is 1, 2 or 3, more preferably p is 2 or 3.

Preferred compounds of general formula (I) are the compounds of Examples 1 to 66 (see section Examples below) and pharmaceutically acceptable salts thereof. Especially preferred are the compounds selected from the group consisting of:

1-Cyclohexylmethyl-5-(4-methoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-5-(3-methoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-2-methyl-5-(4-trifluoromethyl-phenyl)-1H-pyrrole-3-carboxylic acid butylamide,

5-(4-Chloro-phenyl)-1-cyclohexylmethyl-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-2-methyl-5-p-tolyl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-5-(2-methoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-5-(4-fluoro-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-5-(2,4-dimethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

5-(4-Bromo-phenyl)-1-cyclohexylmethyl-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

5-(3-Cyano-phenyl)-1-cyclohexylmethyl-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-5-(2,4-dimethyl-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-5-(4-difluoromethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-2-methyl-5-(4-pyrrolidin-1-yl-phenyl)-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-5-(2,5-dimethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-5-(3,4-difluoro-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

5-(3-Chloro-phenyl)-1-cyclohexylmethyl-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-2-methyl-5-(4-trifluoromethoxy-phenyl)-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-5-(3,4-dimethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

5-(2-Chloro-phenyl)-1-cyclohexylmethyl-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-2-methyl-5-(4-nitro-phenyl)-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-5-(2,5-dimethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid cyclohexylamide,

1-Cyclohexylmethyl-5-(2,5-dimethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid cyclopentylamide,

1-Cyclohexylmethyl-5-(2,5-dimethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid cyclobutylamide,

1-Cyclohexylmethyl-5-(2,5-dimethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid cyclopropylamide,

1-Cyclohexylmethyl-5-(2,5-difluoro-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-5-(4-hydroxy-3-methoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-5-(3-fluoro-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

5-Benzo[1,3]dioxol-5-yl-1-cyclohexylmethyl-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-5-(2,5-dichloro-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

5-(3,5-Bis-trifluoromethyl-phenyl)-1-cyclohexylmethyl-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

5-(3,5-Bis-trifluoromethyl-phenyl)-1-cyclohexylmethyl-2-methyl-1H-pyrrole-3-carboxylic acid cyclohexylamide,

1-Cyclohexylmethyl-2-methyl-5-(4-pyrrolidin-1-yl-phenyl)-1H-pyrrole-3-carboxylic acid cyclohexylamide,

(R)-1-Cyclohexylmethyl-5-(2,5-dimethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid sec-butylamide,

5-(3,5-Bis-trifluoromethyl-phenyl)-1-(4-methoxy-benzyl)-2-methyl-1H-pyrrole-3-carboxylic acid cyclohexylamide,

1-Cyclohexylmethyl-5-(2,5-dimethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid piperidin-1-ylamide,

1-Cyclohexylmethyl-2-methyl-5-pyridin-2-yl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-2-(2-methoxy-phenyl)-5-methyl-1H-imidazole-4-carboxylic acid butylamide,

1-Cyclohexylmethyl-2-(2-methoxy-phenyl)-5-methyl-1H-imidazole-4-carboxylic acid piperidin-1-ylamide,

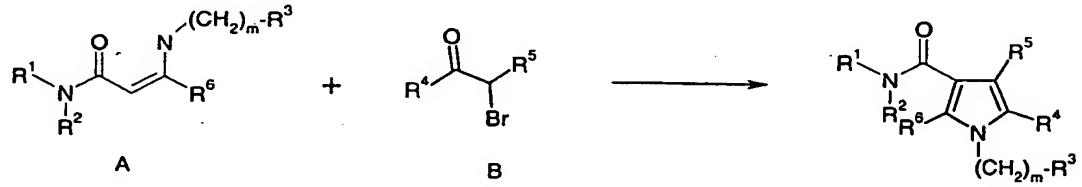
and pharmaceutically acceptable salts thereof.

The present invention also relates to a process for the manufacture of compounds of formula (I) as defined above. The compounds of formula (I) can be manufactured by the methods given below, by the methods given in the Examples or by analogous methods. Appropriate reaction conditions for the individual reaction steps are known to the person skilled in the art. Starting materials are either commercially available or can be prepared by methods analogous to the methods given below or in the Examples or by methods known in the art.

The compounds of formula (I) may be prepared using the general methods described below:

Compounds of formula (I), wherein R^1 to R^6 and m are as previously defined and X = C, can be prepared by reaction of enamines of formula A with alfa-bromoketones of formula B according to methods known in the art (Scheme 1). For example, the reaction can be performed in an inert solvent, such as DMF, in the presence of a hindered base, such as 2,6-di-tert-butylpyridine or 2,6-lutidine.

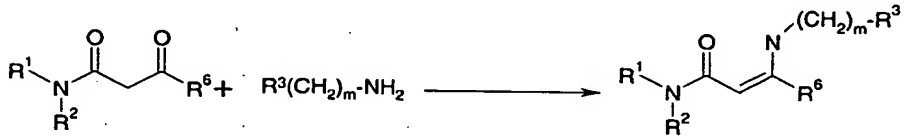
Scheme 1



A B I (X = C)

Enamines of formula A can be prepared from beta-ketoamides of formula C and amines of formula D by methods known in the art (Scheme 2). For example a beta-keto amide of formula C can be reacted with an amine of formula D in a suitable inert solvent (e.g. DMF) in the presence of a hindered base (e.g. 2,6-di-tert-butylpyridine) to yield enamine of formula A.

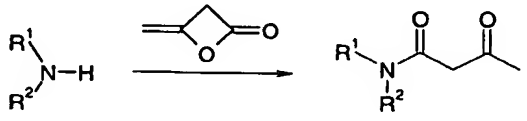
Scheme 2



C D A

Beta-ketoamides of formula C can be purchased from commercial sources or can be prepared by methods known in the art. For example, beta-ketoamides of formula C wherein R^6 = methyl can be prepared by reaction of amines of formula E with diketene in an inert solvent, such as dichloromethane (Scheme 3).

Scheme 3

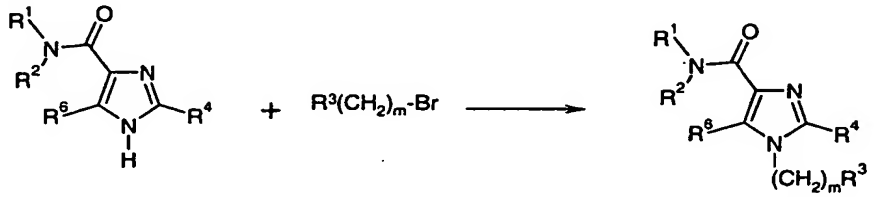


E D

Compounds of formulae B and D are either known from the literature or can be purchased from commercial sources or else can be synthesized by methods known in the art.

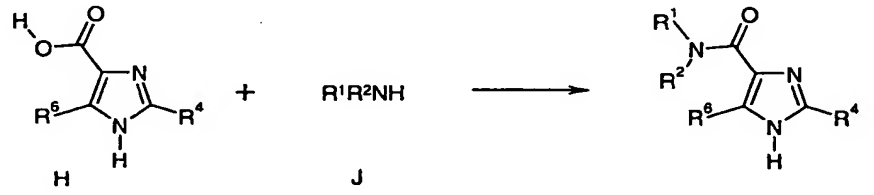
Compounds of formula (I), wherein R^1 to R^6 and m are as previously defined and X = N, can be prepared by alkylation of imidazoles of formula F according to methods known in the art (Scheme 4). For example, imidazoles of formula F may be reacted with alkyl bromides of formula G in the presence of a base (e.g. potassium tert-butylate) in an inert solvent, such as acetonitrile.

Scheme 4



Compounds of formula H can be coupled with an appropriate amine of formula J by methods known in the art (Scheme 5). The reaction can be performed in a suitable inert solvent (e.g. DMF, dichloromethane, pyridine or THF) in the presence of a base (e.g. Hünigs' base) and an activating agent (e.g. TBTU = O-(Benzotriazol-1-yl)-N,N',N'-tetramethyl-uronium-tetrafluoroborat) to yield the corresponding amides of formula F.

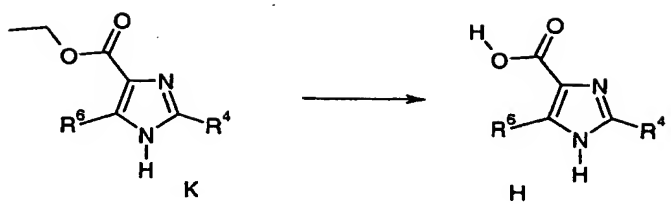
Scheme 5



Compounds of formula H can be obtained by hydrolysis of compounds of formula K by methods known in the art (Scheme 6). For example, the reaction can proceed in a polar solvent (e.g. ethanol) in the presence of a base (e.g. sodium hydroxide).

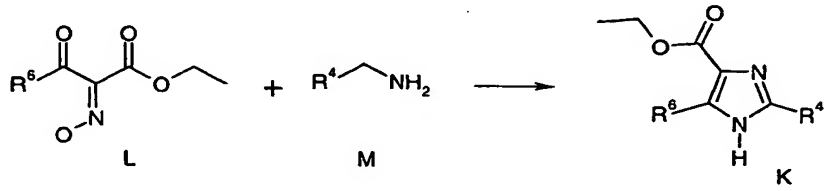
Scheme 6

K



Imidazoles of formula K can be prepared by the reation of 2-oximinoacetoacetates of formula L with an appropriate amine of formula M by methods known in the art (Scheme 7). For example, the reaction can proceed in a polar solvent (e.g. acetonitrile) at elevated temperature.

Scheme 7



Compounds of formula G, J, L and M are either known from the literature or can be purchased from commercial sources or else can be synthesized by methods known in the art.

The invention further relates to compounds of formula (I) as defined above, when manufactured according to a process as defined above.

Some compounds of formula (I) may possess asymmetric centres and are therefore capable of existing in more than one stereoisomeric form. The invention thus also relates to compounds in substantially pure isomeric form at one or more asymmetric centres as well as mixtures, including racemic mixtures, thereof. Such isomers may be prepared by asymmetric synthesis, for example using chiral intermediate, or mixtures may be resolved by conventional mehtods, eg., chromatography (chromatography with a chiral adsorbens or eluent), or use of a solving agent.

It will be appreciated, that the compounds of general formula (I) in this invention may be derivatised at functional groups to provide derivatives which are capable of conversion back to the parent compound in vivo.

As described above, the compounds of formula (I) or pharmaceutically acceptable salts thereof can be used as medicaments for the treatment and/or prophylaxis of diseases which are associated with the modulation of the CB1 receptors.

The invention therefore also relates to pharmaceutical compositions comprising a compound as defined above and a pharmaceutically acceptable carrier and/or adjuvant.

Further, the invention relates to compounds as defined above for use as therapeutic active substances, particularly as therapeutic active substances for the treatment and/or prophylaxis of diseases which are associated with the modulation of CB1 receptors.

In another embodiment, the invention relates to a method for the treatment and/or prophylaxis of diseases which are associated with the modulation of CB1 receptors, which method comprises administering a compound as defined above to a human being or animal.

The invention further relates to the use of compounds as defined above for the treatment and/or prophylaxis of diseases which are associated with the modulation of CB1 receptors.

In addition, the invention relates to the use of compounds as defined above for the preparation of medicaments for the treatment and/or prophylaxis of diseases which are associated with the modulation of CB1 receptors. Such medicaments comprise a compound as defined above.

In this context, the expression 'diseases associated with modulation of CB1 receptors' means diseases which can be treated and/or prevented by modulation of CB1 receptors. Such diseases encompass, but are not limited to, psychic disorders, especially anxiety, psychosis, schizophrenia, depression, abuse of psychotropes, for example for the abuse and/or dependence of a substances, including alcohole dependency and nicotine dependency, neuropathies, migraine, stress, epilepsy, dyskinesias, Parkinson's disease, amnesia, cognitive disorders, senile dementia, Alzheimer's disease, eating disorders, obesity, diabetes type II or non insulin dependent diabetes (NIDD), gastrointestinal diseases, vomiting, diarrhea, urinary disorders, cardiovascular disorders, infertility

disorders, inflammations, infections, cancer, neuroinflammation, in particular in atherosclerosis, or the Guillain-Barré syndrome, viral encephalitis, cerebral vascular incidents and cranial trauma.

In a preferable aspect, the expression 'diseases associated with modulation of CB1 receptors' relates to eating disorders, obesity, diabetes type II or non insulin dependent diabetes (NIDD), neuroinflammation, diarrhea, abuse and/or dependence of a substances, including alcohole dependency and nicotine dependency. In a more preferable aspect, the said term related to eating disorders, obesity, diabetes type II or non insulin dependent diabetes (NIDD), abuse and/or dependence of a substances, including alcohole dependency and nicotine dependency, with obesity being especially preferred.

The following tests were carried out in order to determine the activity of the compounds of formula (I).

The affinity of the compounds of the invention for cannabinoid CB1 receptors was determined using membrane preparations of human embryonic kidney (HEK) cells in which the human cannabis CB1 receptor is transiently transfected using the Semliki Forest Virus system in conjunction with [3H]-CP-55,940 as radioligand. After incubation of a freshly prepared cell membrane preparation with the [3H]-ligand, with or without addition of compounds of the invention, separation of bound and free ligand was performed by filtration over glassfiber filters. Radioactivity on the filter was measured by liquid scintillation counting.

The affinity of the compounds of the invention for cannabinoid CB2 receptors was determined using membrane preparations of human embryonic kidney (HEK) cells in which the human cannabis CB2 receptor is transiently transfected using the Semliki Forest virus system in conjunction with [3H]-CP-55,940 as radioligand. After incubation of a freshly prepared cell membrane preparation with the [3H]-ligand, with or without addition of compounds of the invention, separation of bound of bound and free ligand was performed by filtration over glassfiber filters. Radioactivity on the filter was measured by liquid scintillation counting.

The cannabinoid CB1 antagonistic activity of compounds of the invention was determined by functional studies using CHO cells in which human cannabinoid CB1 receptors are stably expressed (see M. Rinaldi-Carmona et. al., J. Pharmacol. Exp. Ther. 278 (1996) 871). The stable expression of the human cannabinoid receptor in cell systems

was first described in Nature 1990, 346, 561-564 (CB1) and Nature 1993, 365, 61-65 (CB2) respectively. Adenylyl cyclase was stimulated using forskolin and measured by quantifying the amount of accumulated cyclic AMP. Concomitant activation of CB1 receptors by CB1 receptor agonists (e.g. CP-55,940 or (R)-WIN-55212-2) can attenuate the forskolin-induced accumulation of cAMP in a concentration dependent manner. This CB1 receptor mediated response can be antagonised by CB1 receptor antagonists such as the compounds of the invention.

The compounds of formula (I) show an excellent affinity for the CB1 receptor, determined with the experimental conditions described in Devane et.al. Mol. Pharmacol. 34 (1988) 605-613. The compounds of the present invention or the pharmaceutically acceptable salts or sovates are antagonists and selective for the CB1 receptor with affinites below $IC_{50} = 2\ \mu M$. They exhibit at least a 10 fold selectivity against the CB2 receptor.

Compound of Example	IC_{50} [μM]
19	< 2
21	< 2
41	< 2
52	< 2
54	< 2

The compounds of formula (I) and/or their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical preparations for enteral, parenteral or topical administration. They can be administered, for example, perorally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions or infusion solutions, or topically, e.g. in the form of ointments, creams or oils. Oral administration is preferred.

The production of the pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula (I) and/or their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers might, however, be required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar and the like. Suitable carrier materials for injection solutions are, for example, water, alcohols, polyols, glycerol and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavour-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

The dosage of the compounds of formula (I) can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage of about 1 to 1000 mg, especially about 1 to 100 mg, comes into consideration. Depending on severity of the disease and the precise pharmacokinetic profile the compound could be administered with one or several daily dosage units, e.g. in 1 to 3 dosage units.

The pharmaceutical preparations conveniently contain about 1-500 mg, preferably 1-100 mg, of a compound of formula (I).

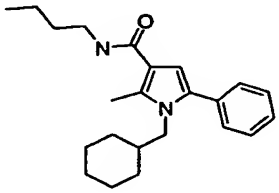
The following Examples serve to illustrate the present invention in more detail. They are, however, not intended to limit its scope in any manner.

Examples

MS = mass spectrometry; ISP = ion spray (positive ion), corresponds to ESI (electrospray, positive ion); mp = melting point; TBTU = O-(Benzotriazol-1-yl)-N,N',N'-tetramethyl-uronium-tetrafluoroborate; DMF = dimethylformamide.

Example 1

1-Cyclohexylmethyl-5-phenyl-2-methyl-1H-pyrrole-3-carboxylic acid butylamide



To a solution of 4.2 g of diketene in dichloromethane (70 ml) cooled at 0°C was added over 1 hour a solution of 3.7 g of butylamine in 50 ml of dichloromethane. The reaction mixture was then stirred for one hour at 0°C and was then allowed to stir at room temperature for another hour. The reaction mixture was concentrated *in vacuo* and the crude residue was partitioned in batches which were directly used in the next step.

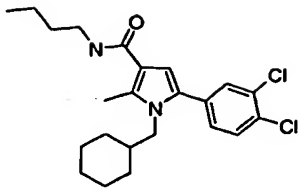
To 2.0 g of the previous crude material in 55 ml of dimethylformamide was added 1.65 ml of cyclohexylmethylamine together with 1.4 ml of trimethyl orthoformate and the reaction mixture was stirred for 24 hours at room temperature.

3.4 ml of the previous solution was then transferred into another reaction vessel and 120 mg of 2-bromo-phenyl-ethanone was added together with 0.092 ml of 2,6-lutidine and the reaction mixture was stirred for another 24 hours at room temperature. After such time the reaction mixture was concentrated *in vacuo* and purified by column chromatography (50 g of SiO_2, n-Heptane – Ethyl acetate 0-80%) to yield 112 mg of the title compound as a light brown gum, MS (ISP) 353.4 $(M+H)^+$.

Examples 2-48 were synthesized in analogy to Example 1, using the indicated educts.

Example 2

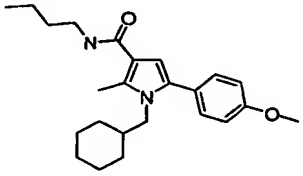
1-Cyclohexylmethyl-5-(3,4-dichloro-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-3',4'-dichloroacetophenone, MS (ISP) 421.4$(M+H)^+$.

Example 3

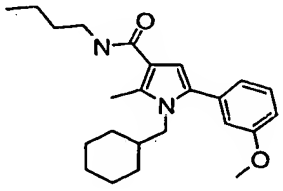
1-Cyclohexylmethyl-5-(4-methoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-4'-acetophenone, MS (ISP) 383.4$(M+H)^+$.

Example 4

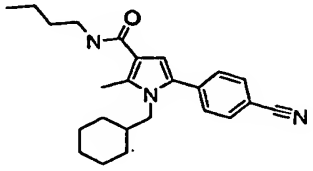
1-Cyclohexylmethyl-5-(3-methoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-3'-methoxyacetophenone, MS (ISP) 383.3$(M+H)^+$.

Example 5

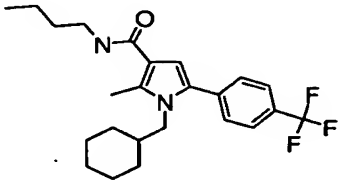
5-(4-Cyano-phenyl)-1-cyclohexylmethyl-2-methyl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-4'cyanoacetophenone, MS (ISP) 378.4$(M+H)^+$.

Example 6

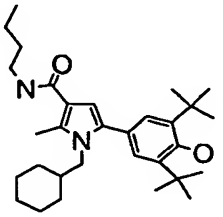
1-Cyclohexylmethyl-2-methyl-5-(4-trifluoromethyl-phenyl)-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-4'-(trifluoromethyl)acetophenone, MS (ISP) 421.4$(M+H)^+$.

Example 7

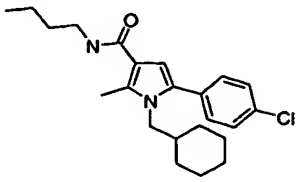
1-Cyclohexylmethyl-5-(3,5-di-tert-butyl-4-hydroxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-1-(3,5-di-tert-butyl-4-hydroxy-phenyl)-ethanone.

Example 8

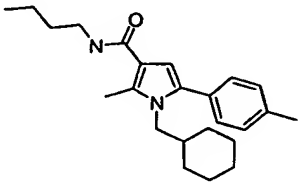
5-(4-Chloro-phenyl)-1-cyclohexylmethyl-2-methyl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-4'-chloroacetophenone, MS (ISP) 387.3$(M+H)^+$.

Example 9

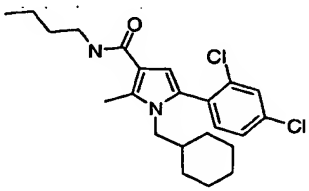
1-Cyclohexylmethyl-2-methyl-5-p-tolyl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-4'-methylacetophenone, MS (ISP) 367.3$(M+H)^+$.

Example 10

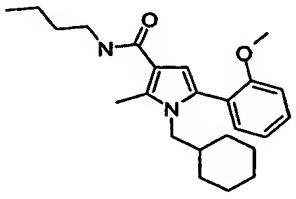
1-Cyclohexylmethyl-5-(2,4-dichloro-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-2',4'-dichloroacetophenone, MS (ISP) 421.2$(M+H)^+$.

Example 11

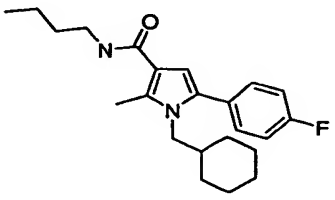
1-Cyclohexylmethyl-5-(2-methoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-2'-methoxyacetophenone, MS (ISP) 383.3$(M+H)^+$.

Example 12

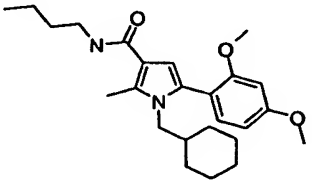
1-Cyclohexylmethyl-5-(4-fluoro-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-4'-fluoroacetophenone, MS (ISP) 371.3$(M+H)^+$.

Example 13

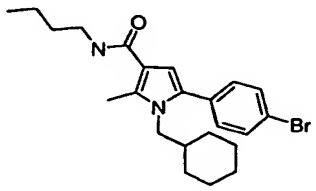
1-Cyclohexylmethyl-5-(2,4-dimethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-2',4'-dimethoxyacetophenone, MS (ISP) 413.4$(M+H)^+$.

Example 14

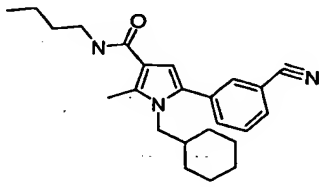
5-(4-Bromo-phenyl)-1-cyclohexylmethyl-2-methyl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-4'-bromoacetophenone, MS (ISP) 433.3$(M+H)^+$.

Example 15

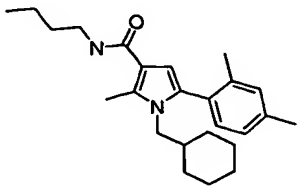
5-(3-Cyano-phenyl)-1-cyclohexylmethyl-2-methyl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-3'-cyanoacetophenone, MS (ISP) 378.4$(M+H)^+$.

Example 16

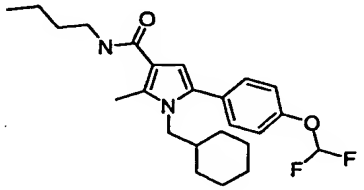
1-Cyclohexylmethyl-5-(2,4-dimethyl-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-2',4'-dimethylacetophenone, MS (ISP) 381.4$(M+H)^+$.

Example 17

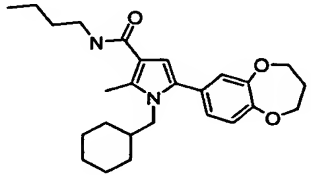
1-Cyclohexylmethyl-5-(4-difluoromethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-4'-(difluoromethoxy)acetophenone, MS (ISP) 419.3$(M+H)^+$.

Example 18

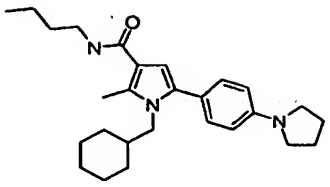
1-Cyclohexylmethyl-5-(3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-1-(3,4-dihydro-2H-1,5-benzodioxepin-7-yl)ethan-1-one, MS (ISP) 425.3 $(M+H)^+$.

Example 19

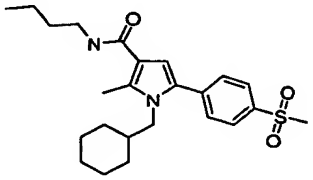
1-Cyclohexylmethyl-2-methyl-5-(4-pyrrolidin-1-yl-phenyl)-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and alpha-bromo-4-(1-pyrrolodino)acetophenone, MS (ISP) 422.4$(M+H)^+$.

Example 20

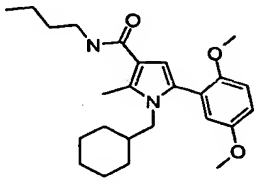
1-Cyclohexylmethyl-5-(4-methanesulfonyl-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-4'-methylsulfonylacetophenone, MS (ISP) 431.4$(M+H)^+$.

Example 21

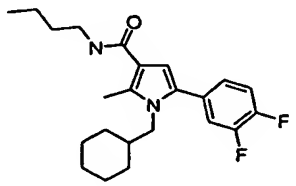
1-Cyclohexylmethyl-5-(2,5-dimethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-2',5'-dimethoxyacetophenone, MS (ISP).

Example 22

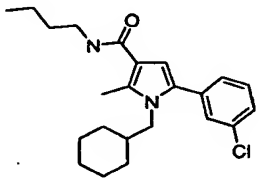
1-Cyclohexylmethyl-5-(3,4-difluoro-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-3',4'-difluoroacetophenone, MS (ISP) 389.3$(M+H)^+$.

Example 23

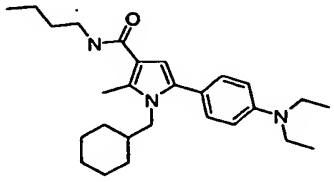
5-(3-Chloro-phenyl)-1-cyclohexylmethyl-2-methyl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-3'chloroacetophenone, MS (ISP) 387.3$(M+H)^+$.

Example 24

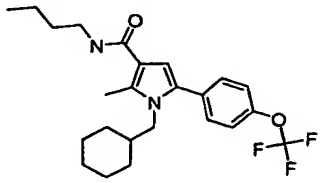
1-Cyclohexylmethyl-5-(4-diethylamino-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-4'-(diethylamino)acetophenone, MS (ISP) 424.4$(M+H)^+$.

Example 25

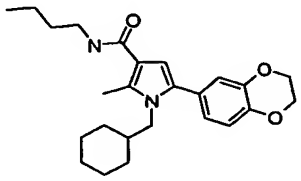
1-Cyclohexylmethyl-2-methyl-5-(4-trifluoromethoxy-phenyl)-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-4'-(trifluoromethoxy)acetophenone, MS (ISP) 437.3$(M+H)^+$.

Example 26

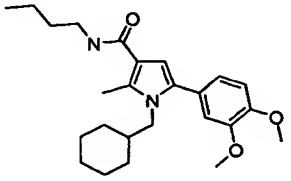
1-Cyclohexylmethyl-5-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-1-(2,3-dihydro-1,4-benzodioxin-6-yl)ethan-1-one, MS (ISP) 411.3$(M+H)^+$.

Example 27

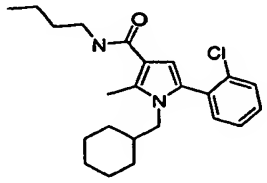
1-Cyclohexylmethyl-5-(3,4-dimethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-3',4'-dimethoxyacetophenone, MS (ISP) 413.4$(M+H)^+$.

Example 28

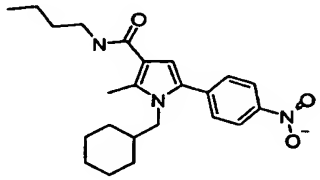
5-(2-Chloro-phenyl)-1-cyclohexylmethyl-2-methyl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-2'-chloroacetophenone, MS (ISP) 387.3$(M+H)^+$.

Example 29

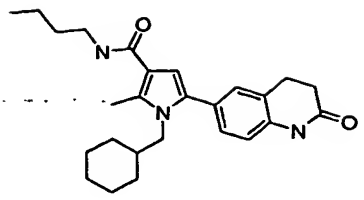
1-Cyclohexylmethyl-2-methyl-5-(4-nitro-phenyl)-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-4'-nitroacetophenone, MS (ISP) 398.3$(M+H)^+$.

Example 30

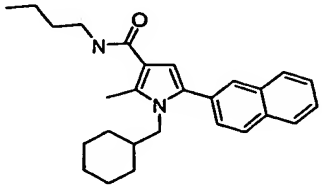
1-Cyclohexylmethyl-2-methyl-5-(2-oxo-1,2,3,4-tetrahydro-quinolin-6-yl)-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 6-(2-bromo-acetyl)-3,4-dihydro-1H-quinolin-2-one, MS (ISP) 422.3$(M+H)^+$.

Example 31

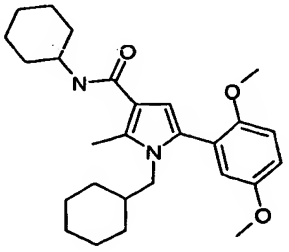
1-Cyclohexylmethyl-2-methyl-5-naphthalen-2-yl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and bromomethyl-2-naphthylketone, MS (ISP) 403.4$(M+H)^+$.

Example 32

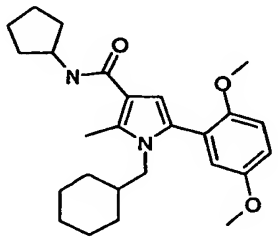
1-Cyclohexylmethyl-5-(2,5-dimethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid cyclohexylamide



The title compound was obtained using cyclohexylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-2',5'-dimethoxyacetophenone, MS (ISP) 439.4$(M+H)^+$.

Example 33

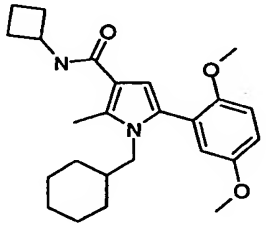
1-Cyclohexylmethyl-5-(2,5-dimethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid cyclopentylamide



The title compound was obtained using cyclopentylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-2',5'-dimethoxyacetophenone, MS (ISP) 425.3$(M+H)^+$.

Example 34

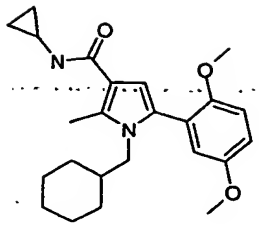
1-Cyclohexylmethyl-5-(2,5-dimethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid cyclobutylamide



The title compound was obtained using cyclobutylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-2',5'-dimethoxyacetophenone, MS (ISP) 411.3$(M+H)^+$.

Example 35

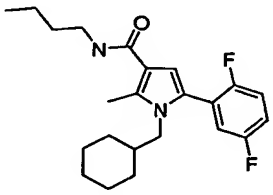
1-Cyclohexylmethyl-5-(2,5-dimethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid cyclopropylamide



The title compound was obtained using cycloproplyamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-2',5'-dimethoxyacetophenone, MS (ISP) 397.3$(M+H)^+$.

Example 36

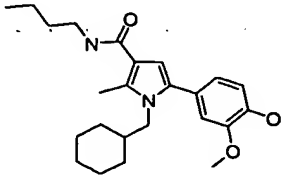
1-Cyclohexylmethyl-5-(2,5-difluoro-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-2',5'-difluoroacetophenone.

Example 37

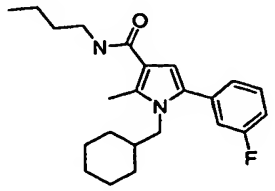
1-Cyclohexylmethyl-5-(4-hydroxy-3-methoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-3'methoxy-4'-hydroxyacetophenone.

Example 38

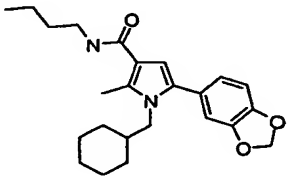
1-Cyclohexylmethyl-5-(3-fluoro-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-3'-fluoroacetophenone.

Example 39

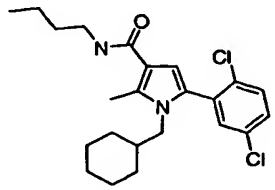
5-Benzo[1,3]dioxol-5-yl-1-cyclohexylmethyl-2-methyl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 1-(1,3-bentodioxol-5-yl)-2-bromoethan-1-one.

Example 40

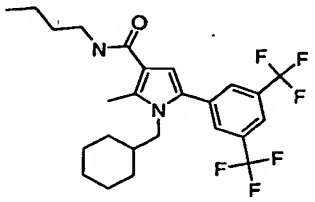
1-Cyclohexylmethyl-5-(2,5-dichloro-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-2',5'-dichloroacetophenone.

Example 41

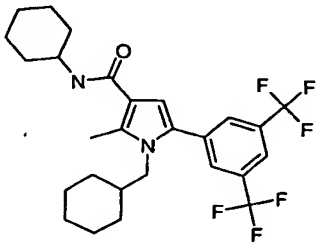
5-(3,5-Bis-trifluoromethyl-phenyl)-1-cyclohexylmethyl-2-methyl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-3',5'-di(trifluoromethyl)acetophenone.

Example 42

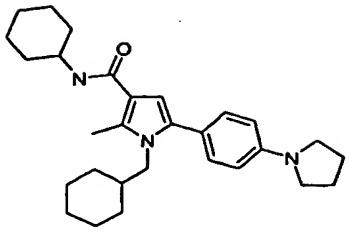
5-(3,5-Bis-trifluoromethyl-phenyl)-1-cyclohexylmethyl-2-methyl-1H-pyrrole-3-carboxylic acid cyclohexylamide



The title compound was obtained using cyclohexylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-3',5'-di(trifluoromethyl)acetophenone, MS (ISP) 515.3$(M+H)^+$.

Example 43

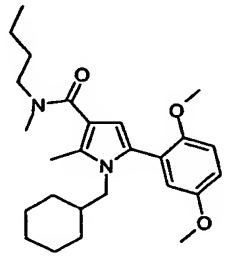
1-Cyclohexylmethyl-2-methyl-5-(4-pyrrolidin-1-yl-phenyl)-1H-pyrrole-3-carboxylic acid cyclohexylamide



The title compound was obtained using cyclohexylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and , MS (ISP) 448.4$(M+H)^+$.

Example 44

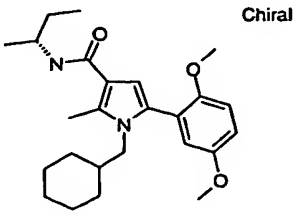
1-Cyclohexylmethyl-5-(2,5-dimethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butyl-methyl-amide



The title compound was obtained using N-methylbutylamine as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-2',5'-dimethoxyacetophenone, MS (ISP) 427.3$(M+H)^+$.

Example 45

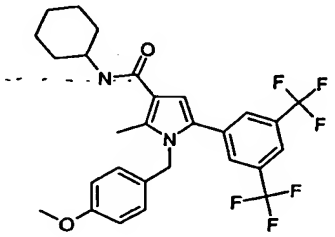
(R)-1-Cyclohexylmethyl-5-(2,5-dimethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid sec-butylamide



The title compound was obtained using (R)-(-)-2-Aminobutane as R^1R^2NH, aminoethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-2',5'-dimethoxyacetophenone, MS (ISP) 413.3$(M+H)^+$.

Example 46

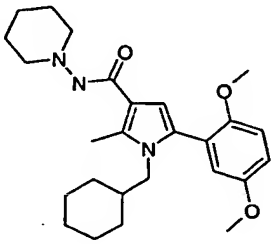
5-(3,5-Bis-trifluoromethyl-phenyl)-1-(4-methoxy-benzyl)-2-methyl-1H-pyrrole-3-carboxylic acid cyclohexylamide



The title compound was obtained using cyclohexylamine as R^1R^2NH, 4-methoxybenzylamine as R^3-$(CH_2)_m$-NH_2 and 2-bromo-3',5'-di(trifluoromethyl)-acetophenone, MS (ISP) 539.5$(M+H)^+$.

Example 47

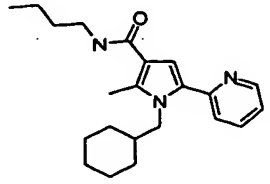
1-Cyclohexylmethyl-5-(2,5-dimethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid piperidin-1-ylamide



The title compound was obtained using 1-aminopiperidine as R^1R^2NH, aminomethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-bromo-2',5'-dimethoxyacetophenone, MS (ISP) 440.5$(M+H)^+$.

Example 48

1-Cyclohexylmethyl-2-methyl-5-pyridin-2-yl-1H-pyrrole-3-carboxylic acid butylamide



The title compound was obtained using butylamine as R^1R^2NH, aminomethylcyclohexane as R^3-$(CH_2)_m$-NH_2 and 2-(bromoacetyl)pyridine, MS (ISP) 354.3$(M+H)^+$.

Example 49

1-Cyclohexylmethyl-2-(2-chloro-phenyl)-5-methyl-1H-imidazole-4-carboxylic acid butylamide

Preparation of 2-(2-Chloro-phenyl)-5-methyl-1H-imidazole-4-carboxylic acid ethyl ester:

To a solution of 8.5 g of ethyl 2-oximinoacetoacetate in acetonitrile (100 ml) was added 7.5 ml of 2-chlorobenzylamine. The reaction mixture was then refluxed for 4 hours under argon atmosphere. After such time the reaction mixture was then concentrated *in vacuo* and the residue was triturated with warm ethylacetate for 10 minutes. After allowing to cool down to room temperature the solid was filtered and dried *in vacuo* to yield 11.3 g of a white powder, MS (ISP) 265.1 $(M+H)^+$.

Preparation of 2-(2-Chloro-phenyl)-5-methyl-1H-imidazole-4-carboxylic acid:

To 11.2 g of 2-(2-chloro-phenyl)-5-methyl-1H-imidazole-4-carboxylic acid ethyl ester in 150 ml of ethanol was added 80 ml of a 2N-NaOH solution and the reaction mixture was stirred at 95° C for 17 hours. After such time ethanol was removed *in vacuo* and the remaining aqueous solution was treated with a 2N HCl solution until obtaining pH=3. The precipitate was filtered and dried under high vacuum to yield 9.0 g of a pale yellow powder.

Preparation of 2-(2-Chloro-phenyl)-5-methyl-1H-imidazole-4-carboxylic acid piperidin-1-ylamide:

To 1 g of 2-(2-chloro-phenyl)-5-methyl-1H-imidazole-4-carboxylic acid in 10 ml of DMF was added 1.36 g of TBTU and 3.6 ml of Hünigs' base and the reaction mixture was stirred for 1 minute. Then 0.46 ml of 1-aminopiperidin was added and the reaction mixture was stirred for 1.5 hour at room temperature. After such time the reaction mixture was poured

onto 200 ml of water and extracted with ethyl acetate (2 x 200 ml). The combined organic extracts were then washed with water (2 x 100 ml) and brine (50 ml), dried ($MgSO_4$) and concentrated *in vacuo* to yield an oil which crystallized on standing. The residue was then triturated with heptane, the solid was filtered and dried to yield 1.12 g of the title compound, MS (ISP) 319.0 $(M+H)^+$.

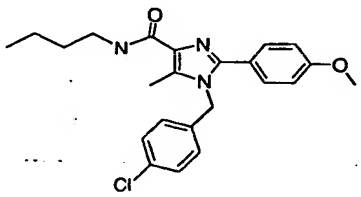
Preparation of 1-Cyclohexylmethyl-2-(2-chloro-phenyl)-5-methyl-1H-imidazole-4-carboxylic acid butylamide

To a suspension of 90 mg of 2-(2-chloro-phenyl)-5-methyl-1H-imidazole-4-carboxylic acid piperidin-1-ylamide in 4 ml of acetonitrile was added 35 mg of potassium tert-butylate and the reaction mixture was stirred at room temperature for 2 minutes. After such time, 0.04 ml of (bromomethyl)cyclohexane was added and the reaction mixture was stirred at 80°C for 28 hours under argon atmosphere. The reaction mixture was then concentrated *in vacuo* and purified by column chromatography (SiO_2, Heptane/EtOAC : 1/1) to give 64 mg of the title compound as a pale yellow solid, MS (ISP) 415.3 $(M+H)^+$.

Examples 50-66 were synthesized in analogy to example 49, using the indicated educts.

Example 50

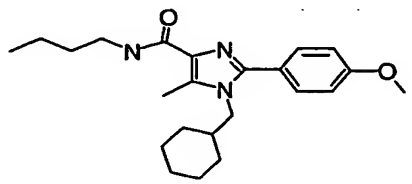
1-(4-Chloro-benzyl)-2-(4-methoxy-phenyl)-5-methyl-1H-imidazole-4-carboxylic acid butylamide



The title compound was obtained using 4-Methoxy benzylamine as R^4-CH_2-NH_2, Butylamine as R^1R^2NH and 4-Chlorobenzyl chloride as R^3-$(CH_2)_m$-Br, MS (ISP) 412.3$(M+H)^+$.

Example 51

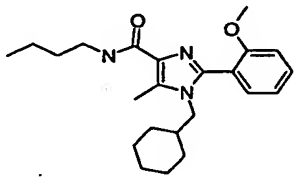
1-Cyclohexylmethyl-2-(4-methoxy-phenyl)-5-methyl-1H-imidazole-4-carboxylic acid butylamide



The title compound was obtained using 4-Methoxy benzylamine as R^4-CH_2-NH_2, Butylamine as R^1R^2NH and (Bromomethyl) cyclohexane as R^3-$(CH_2)_m$-Br, MS (ISP) 384.3$(M+H)^+$.

Example 52

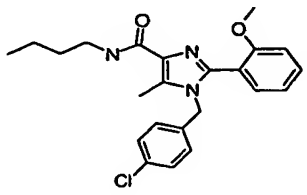
1-Cyclohexylmethyl-2-(2-methoxy-phenyl)-5-methyl-1H-imidazole-4-carboxylic acid butylamide



The title compound was obtained using 2-Methoxy benzylamine as R^4-CH_2-NH_2, Butylamine as R^1R^2NH and (Bromomethyl) cyclohexane as R^3-$(CH_2)_m$-Br, MS (ISP) 384.3$(M+H)^+$.

Example 53

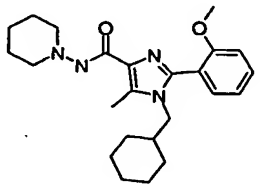
1-(4-Chloro-benzyl)-2-(2-methoxy-phenyl)-5-methyl-1H-imidazole-4-carboxylic acid butylamide



The title compound was obtained using 2-Methoxy benzylamine as R^4-CH_2-NH_2, Butylamine as R^1R^2NH and 4-Chlorobenzyl chloride as R^3-$(CH_2)_m$-Br, MS (ISP) 412.3$(M+H)^+$.

Example 54

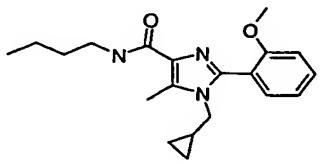
1-Cyclohexylmethyl-2-(2-methoxy-phenyl)-5-methyl-1H-imidazole-4-carboxylic acid piperidin-1-ylamide



The title compound was obtained using 2-Methoxy benzylamine as R^4-CH_2-NH_2, 1-Aminopiperidine as R^1R^2NH and (Bromomethyl) cyclohexane as R^3-$(CH_2)_m$-Br, MS (ISP) 411.4$(M+H)^+$.

Example 55

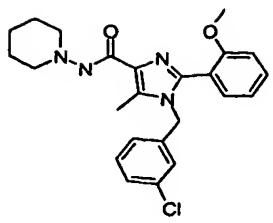
1-Cyclopropylmethyl-2-(2-methoxy-phenyl)-5-methyl-1H-imidazole-4-carboxylic acid butylamide



The title compound was obtained using 2-Methoxy benzylamine as R^4-CH_2-NH_2, Butylamine as R^1R^2NH and Bromomethyl cyclopropane as R^3-$(CH_2)_m$-Br, MS (ISP) 342.2$(M+H)^+$.

Example 56

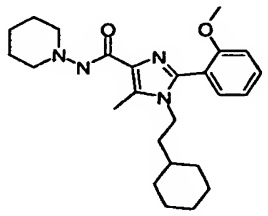
1-(3-Chloro-benzyl)-2-(2-methoxy-phenyl)-5-methyl-1H-imidazole-4-carboxylic acid piperidin-1-ylamide



The title compound was obtained using 2-Methoxy benzylamine as R^4-CH_2-NH_2, 1-Aminopiperidine as R^1R^2NH and 3-Chlorobenzylchloride as R^3-$(CH_2)_m$-Br, MS (ISP) 439.2$(M+H)^+$.

Example 57

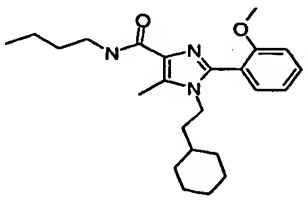
1-(2-Cyclohexyl-ethyl)-2-(2-methoxy-phenyl)-5-methyl-1H-imidazole-4-carboxylic acid piperidin-1-ylamide



The title compound was obtained using 2-Methoxy benzylamine as R^4-CH_2-NH_2, 1-Aminopiperidine as R^1R^2NH and (Bromoethyl) cyclohexane as R^3-$(CH_2)_m$-Br, MS (ISP) 425.3$(M+H)^+$.

Example 58

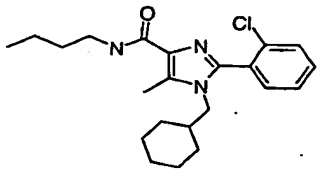
1-(2-Cyclohexyl-ethyl)-2-(2-methoxy-phenyl)-5-methyl-1H-imidazole-4-carboxylic acid butylamide



The title compound was obtained using 2-Methoxy benzylamine as R^4-CH_2-NH_2, Butylamine as R^1R^2NH and (Bromoethyl) cyclohexane as R^3-$(CH_2)_m$-Br, MS (ISP) 398.3$(M+H)^+$.

Example 59

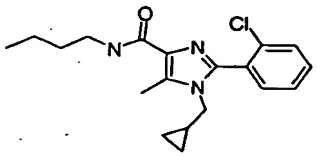
2-(2-Chloro-phenyl)-1-cyclohexylmethyl-5-methyl-1H-imidazole-4-carboxylic acid butylamide



The title compound was obtained using 2-Chloro benzylamine as R^4-CH_2-NH_2, Butylamine as R^1R^2NH and (Bromomethyl) cyclohexane as R^3-$(CH_2)_m$-Br, MS (ISP) 388.2$(M+H)^+$.

Example 60

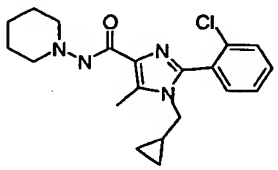
2-(2-Chloro-phenyl)-1-cyclopropylmethyl-5-methyl-1H-imidazole-4-carboxylic acid butylamide



The title compound was obtained using 2-Chloro benzylamine as R^4-CH_2-NH_2, Butylamine as R^1R^2NH and Bromomethyl cyclopropane as R^3-$(CH_2)_m$-Br, MS (ISP) 346.1$(M+H)^+$.

Example 61

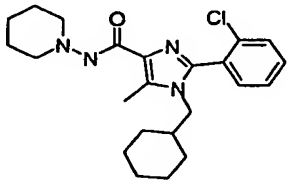
2-(2-Chloro-phenyl)-1-cyclopropylmethyl-5-methyl-1H-imidazole-4-carboxylic acid piperidin-1-ylamide



The title compound was obtained using 2-Chloro benzylamine as R^4-CH_2-NH_2, 1-Aminopiperidine as R^1R^2NH and Bromomethyl cyclopropane as R^3-$(CH_2)_m$-Br, MS (ISP) 373.2$(M+H)^+$.

Example 62

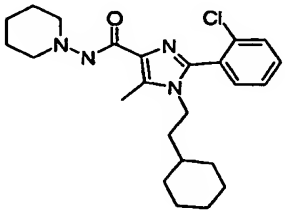
2-(2-Chloro-phenyl)-1-cyclohexylmethyl-5-methyl-1H-imidazole-4-carboxylic acid piperidin-1-ylamide



The title compound was obtained using 2-Chloro benzylamine as R^4-CH_2-NH_2, 1-Aminopiperidine as R^1R^2NH and (Bromomethyl) cyclohexane as R^3-$(CH_2)_m$-Br, MS (ISP) 415.3$(M+H)^+$.

Example 63

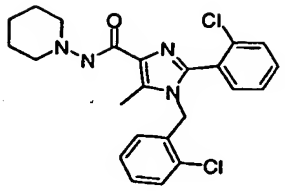
2-(2-Chloro-phenyl)-1-(2-cyclohexyl-ethyl)-5-methyl-1H-imidazole-4-carboxylic acid piperidin-1-ylamide



The title compound was obtained using 2-Chloro benzylamine as R^4-CH_2-NH_2, 1-Aminopiperidine as R^1R^2NH and (Bromoethyl) cyclohexane as R^3-$(CH_2)_m$-Br, MS (ISP) 429.4$(M+H)^+$.

Example 64

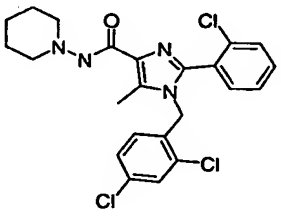
1-(2-Chloro-benzyl)-2-(2-chloro-phenyl)-5-methyl-1H-imidazole-4-carboxylic acid piperidin-1-ylamide



The title compound was obtained using 2-Chloro benzylamine as R^4-CH_2-NH_2, 1-Aminopiperidine as R^1R^2NH and 2-Chlorobenzylbromide as R^3-$(CH_2)_m$-Br, MS (ISP) 443.3$(M+H)^+$.

Example 65

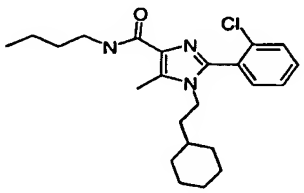
2-(2-Chloro-phenyl)-1-(2,4-dichloro-benzyl)-5-methyl-1H-imidazole-4-carboxylic acid piperidin-1-ylamide



The title compound was obtained using 2-Chloro benzylamine as R^4-CH_2-NH_2, 1-Aminopiperidine as R^1R^2NH and 2,4-Dichlorobenzylchlorid as R^3-$(CH_2)_m$-Br, MS (ISP) 477.2$(M+H)^+$.

Example 66

2-(2-Chloro-phenyl)-1-(2-cyclohexyl-ethyl)-5-methyl-1H-imidazole-4-carboxylic acid butylamide



The title compound was obtained using 2-Chloro benzylamine as R^4-CH_2-NH_2, Butylamine as R^1R^2NH and (Bromoethyl) cyclohexane as R^3-$(CH_2)_m$-Br, MS (ISP) 402.4$(M+H)^+$.

Galenical Examples

Example A

Film coated tablets containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per tablet	
Kernel:		
Compound of formula (I)	10.0 mg	200.0 mg
Microcrystalline cellulose	23.5 mg	43.5 mg
Lactose hydrous	60.0 mg	70.0 mg
Povidone K30	12.5 mg	15.0 mg
Sodium starch glycolate	12.5 mg	17.0 mg
Magnesium stearate	1.5 mg	4.5 mg
(Kernel Weight)	120.0 mg	350.0 mg
Film Coat:		
Hydroxypropyl methyl cellulose	3.5 mg	7.0 mg
Polyethylene glycol 6000	0.8 mg	1.6 mg
Talc	1.3 mg	2.6 mg
Iron oxyde (yellow)	0.8 mg	1.6 mg
Titan dioxide	0.8 mg	1.6 mg

The active ingredient is sieved and mixed with microcrystalline cellulose and the mixture is granulated with a solution of polyvinylpyrrolidone in water. The granulate is mixed with sodium starch glycolate and magesium stearate and compressed to yield kernels of 120 or 350 mg respectively. The kernels are lacquered with an aq. solution / suspension of the above mentioned film coat.

Example B

Capsules containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per capsule
Compound of formula (I)	25.0 mg
Lactose	150.0 mg
Maize starch	20.0 mg
Talc	5.0 mg

The components are sieved and mixed and filled into capsules of size 2.

Example C

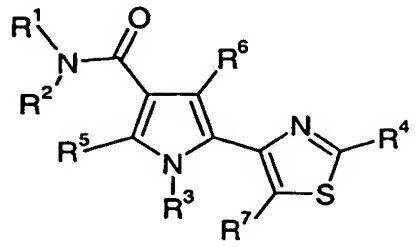
Injection solutions can have the following composition:

Compound of formula (I)	3.0 mg
Polyethylene glycol 400	150.0 mg
Acetic acid	q.s. ad pH 5.0
Water for injection solutions	ad 1.0 ml

The active ingredient is dissolved in a mixture of Polyethylene glycol 400 and water for injection (part). The pH is adjusted to 5.0 by addition of acetic acid. The volume is adjusted to 1.0 ml by addition of the residual amount of water. The solution is filtered, filled into vials using an appropriate overage and sterilized.

Claims

1. Compounds of formula (I)



(I)

wherein

X is C or N ;

R^1 is hydrogen or lower alkyl;

R^2 is lower alkyl or $-(CH_2)_n-R^{2a}$;

R^{2a} is cycloalkyl, optionally mono-, di-, tri- or tetra-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, fluorinated lower alkyl or fluorinated lower alkoxy; a 5- or 6-membered monovalent saturated heterocyclic ring containing one to three heteroatoms independently selected from nitrogen, oxygen and sulfur, said heterocyclic ring being optionally mono-, di- or tri-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, amino, lower alkylamino, cycloalkyl, oxo, fluorinated lower alkyl or fluorinated lower alkoxy; a 5- or 6-membered monovalent heteroaromatic ring containing one to four heteroatoms independently selected from nitrogen, oxygen and sulfur, said heteroaromatic ring being optionally mono-, di- or tri-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, halogen, amino, lower alkylamino or cycloalkyl; or phenyl, which may optionally be mono-, di- or tri-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, halogen, lower alkylamino, halogenated lower alkyl, halogenated lower alkoxy or nitro;

R^3 is cycloalkyl, optionally mono-, di-, tri- or tetra-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, fluorinated lower alkyl or fluorinated lower alkoxy; or phenyl, which may optionally be mono-, di- or tri-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, halogen, lower alkylamino, halogenated lower alkyl, halogenated lower alkoxy or nitro;

R^4 is a 5- or 6-membered monovalent heteroaromatic ring containing one to three heteroatoms independently selected from nitrogen, oxygen and sulfur, said heteroaromatic ring being optionally mono-, di- or tri-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, halogen, amino, lower alkylamino; naphthyl, which may optionally be mono-, di- or tri-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, halogen, lower alkylamino, halogenated lower alkyl, halogenated lower alkoxy or nitro; or phenyl which may optionally be mono-, di- or tri-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, halogen, nitro, halogenated lower alkyl, halogenated lower alkoxy, cyano, lower alkylsulfonyl or $-NR^7R^8$; or two adjacent substituents of the said phenyl residue together are $-O-(CH_2)_p-O-$ or $-(CH_2)_2-C(O)NH-$;

R^5 and R^6 are each independently hydrogen, lower alkyl, halogen or fluorinated methyl;

R^7 and R^8 are each independently hydrogen or lower alkyl; or R^7 and R^8 together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated or aromatic heterocyclic ring optionally containing one or two further heteroatoms independently selected from nitrogen, oxygen and sulfur, said saturated or aromatic heterocyclic ring being optionally substituted by hydroxy, lower alkyl, lower alkoxy, halogen, amino or lower alkylamino;

m is 0, 1 or 2;

n is 0 or 1;

p is 1, 2 or 3;

and pharmaceutically acceptable salts thereof.

2. Compounds according to claim 1, wherein R^1 is hydrogen.

3. Compounds according to any of claims 1 or 2, wherein R^2 is lower alkyl or $-(CH_2)_n-R^{2a}$.

4. Compounds according to claim 3, wherein R^{2a} is a cycloalkyl residues with three to six carbon atoms which may optionally be mono-, di-, tri- or tetra-substituted, independently, by lower alkyl and/or hydroxy.

5. Compounds according to claim 3, wherein R^{2a} is a 5-membered heterocyclic ring containing one or two heteroatoms independently selected from nitrogen and oxygen,

said heterocyclic ring being optionally mono-, di- or tri-substituted, independently, by lower alkyl or by oxo.

6. Compounds according to claim 3, wherein R^{2a} is a 5- or 6-membered heteroaromatic ring containing one, two or four heteroatoms independently selected from nitrogen, oxygen and sulfur, said heteroaromatic ring being optionally mono-substituted by lower alkyl or by cycloalkyl.

7. Compounds according to claim 3, wherein R^{2a} is a phenyl residue which is optionally mono- or di-substituted, independently, by lower alkoxy, halogen, halogenated lower alkyl, halogenated lower alkoxy or nitro.

8. Compounds according to any of claims 1 to 7, wherein R^3 is an unsubstituted cycloalkyl residue with five or six carbon atoms.

9. Compounds according to any of claims 1 to 7, wherein R^3 is a phenyl residue which is optionally mono- or di-substituted, independently, by lower alkoxy, halogen, halogenated lower alkyl, halogenated lower alkoxy or nitro.

10. Compounds according to any of claims 1 to 9, wherein R^4 is a 6-membered heteroaromatic ring containing one or two nitrogen atoms, said heteroaromatic ring being optionally mono-substituted by lower alkyl.

11. Compounds according to any of claims 1 to 9, wherein R^4 is phenyl optionally mono-, di- or tri-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, halogen, nitro, halogenated lower alkyl, halogenated lower alkoxy, cyano, lower alkylsulfonyl, or by a residue $-NR^7R^8$.

12. Compounds according to any of claims 1 to 9, wherein two adjacent substituents of a phenyl residue R^4 together are $-O-(CH_2)_p-O-$ or $-(CH_2)_2-C(O)NH-$, and p is 2 or 3.

13. Compounds according to claim 12, wherein both R^7 and R^8 are methyl or both R^7 and R^8 are ethyl.

14. Compounds according to claim 12, wherein R^7 and R^8 together with the nitrogen atom to which they are attached form a 5-membered, saturated heterocyclic ring optionally containing one further heteroatom independently selected from nitrogen and oxygen, said saturated or aromatic heterocyclic ring being optionally mono-substituted by lower alkyl.

15. Compounds according to any of claims 1 to 14, wherein X is C.

16. Compounds according to any of claims 1 to 14, wherein X is N.

17. Compounds according to any of claims 1 to 16, selected from the group consisting of:

1-Cyclohexylmethyl-5-(4-methoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-5-(3-methoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-2-methyl-5-(4-trifluoromethyl-phenyl)-1H-pyrrole-3-carboxylic acid butylamide,

5-(4-Chloro-phenyl)-1-cyclohexylmethyl-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-2-methyl-5-p-tolyl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-5-(2-methoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-5-(4-fluoro-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-5-(2,4-dimethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

5-(4-Bromo-phenyl)-1-cyclohexylmethyl-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

5-(3-Cyano-phenyl)-1-cyclohexylmethyl-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-5-(2,4-dimethyl-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-5-(4-difluoromethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-2-methyl-5-(4-pyrrolidin-1-yl-phenyl)-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-5-(2,5-dimethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-5-(3,4-difluoro-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

5-(3-Chloro-phenyl)-1-cyclohexylmethyl-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-2-methyl-5-(4-trifluoromethoxy-phenyl)-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-5-(3,4-dimethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

5-(2-Chloro-phenyl)-1-cyclohexylmethyl-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-2-methyl-5-(4-nitro-phenyl)-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-5-(2,5-dimethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid cyclohexylamide,

1-Cyclohexylmethyl-5-(2,5-dimethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid cyclopentylamide,

1-Cyclohexylmethyl-5-(2,5-dimethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid cyclobutylamide,

1-Cyclohexylmethyl-5-(2,5-dimethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid cyclopropylamide,

1-Cyclohexylmethyl-5-(2,5-difluoro-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-5-(4-hydroxy-3-methoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-5-(3-fluoro-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

5-Benzo[1,3]dioxol-5-yl-1-cyclohexylmethyl-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

1-Cyclohexylmethyl-5-(2,5-dichloro-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

5-(3,5-Bis-trifluoromethyl-phenyl)-1-cyclohexylmethyl-2-methyl-1H-pyrrole-3-carboxylic acid butylamide,

5-(3,5-Bis-trifluoromethyl-phenyl)-1-cyclohexylmethyl-2-methyl-1H-pyrrole-3-carboxylic acid cyclohexylamide,

1-Cyclohexylmethyl-2-methyl-5-(4-pyrrolidin-1-yl-phenyl)-1H-pyrrole-3-carboxylic acid cyclohexylamide,

(R)-1-Cyclohexylmethyl-5-(2,5-dimethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid sec-butylamide,

5-(3,5-Bis-trifluoromethyl-phenyl)-1-(4-methoxy-benzyl)-2-methyl-1H-pyrrole-3-carboxylic acid cyclohexylamide,

1-Cyclohexylmethyl-5-(2,5-dimethoxy-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid piperidin-1-ylamide,

1-Cyclohexylmethyl-2-methyl-5-pyridin-2-yl-1H-pyrrole-3-carboxylic acid butylamide,

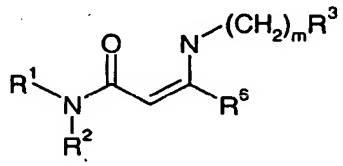
1-Cyclohexylmethyl-2-(2-methoxy-phenyl)-5-methyl-1H-imidazole-4-carboxylic acid butylamide,

1-Cyclohexylmethyl-2-(2-methoxy-phenyl)-5-methyl-1H-imidazole-4-carboxylic acid piperidin-1-ylamide,

and pharmaceutically acceptable salts thereof.

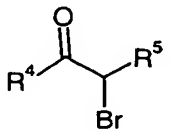
18. A process for the manufacture of compounds of formula (I) as defined in any of claims 1 to 16, which process comprises:

(a) reaction of an enamine of formula A:



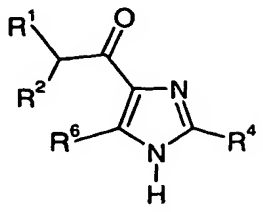
wherein R^1, R^2, R^3, R^6 and m are as defined claim 1;

with an alfa-bromoketone of formula B:



wherein R^4 and R^5 are as defined claim 1; or

(b) alkylation of an imidazole of formula F:



wherein R^1, R^2, R^4 and R^6 are as defined claim 1;

with an alkyl bromide of formula G:

$$R^3(CH_2)_m\text{-}Br$$

wherein R^3 and m are as defined claim 1.

19. Compounds according to any of claims 1 to 17 when manufactured by a process according to claim 18.

20. Pharmaceutical compositions comprising a compound according to any of claims 1 to 17 and a pharmaceutically acceptable carrier and/or adjuvant.

21. Compounds according to any of claims 1 to 17 for use as therapeutic active substances.

22. Compounds according to any of claims 1 to 17 for use as therapeutic active substances for the treatment and/or prophylaxis of diseases which are associated with modulation of the CB1 receptor.

23. A method for the treatment and/or prophylaxis of diseases which are associated with the modulation of the CB1 receptors which method comprises administering a compound according to any of claims 1 to 17 to a human being or animal.

24. The use of compounds according to any of claims 1 to 17 for the treatment and/or prophylaxis of diseases which are associated with the modulation of CB1 receptors.

25. The use of compounds according to any of claims 1 to 17 for the preparation of medicaments for the treatment and/or prophylaxis of diseases which are associated with the modulation of CB1 receptors.

26. The novel compounds, processes and methods as well as the use of such compounds substantially as described hereinbefore.

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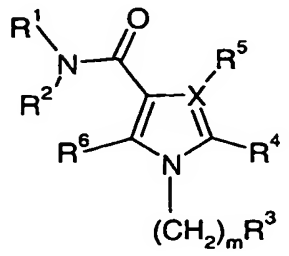
Abstract

The present invention relates to compounds of formula (I)



(I)

wherein R^1, R^2, R^3, R^4, R^5, R^6, m and X are as defined in the description and claims, and pharmaceutically acceptable salts thereof. The compounds are useful for the treatment and/or prophylaxis of diseases which are associated with the modulation ot CB1 receptors.

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